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No. 07- 07-838

IN THE

Supreme Court of the United States

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Petitioners,

v.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

EDGAR H. HAUG
Counsel of Record
KEVIN MURPHY
JEFFREY A. HOVDEN
DAVID A. ZWALLY
FROMMER LAWRENCE & HAUG LLP
745 Fifth Avenue
New York, New York 10151
(212) 588-0800

Attorneys for Petitioners

213035

COUNSEL PRESS
(800) 274-3321 • (800) 359-6859

QUESTION PRESENTED

In *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007), this Court reaffirmed its earlier precedents governing whether an invention is obvious to one skilled in the art and therefore unpatentable. Before this Court's ruling in *KSR*, courts would seek in the prior art proof of a "teaching, suggestion, or motivation" ("TSM") to combine prior-art teachings in order to conclude a patent was obvious. Observing that the TSM test was based neither in Supreme Court precedent nor statute (35 U.S.C. § 103(a)), this Court unanimously reversed, holding that the obviousness analysis was "flexible" and need not "seek out precise teachings directed to the specific subject matter of the challenged claim." *Id.* at 1739, 1741. Obviousness depends instead on the "objective reach" of the claim. *Id.* at 1742. "If the claim extends to what is obvious, it is invalid under § 103." *Id.*

In this case—despite this Court's holding in *KSR*—the Federal Circuit rigidly applied the TSM test to hold that obvious compounds were not obvious. The patent at issue, U.S. Patent No. 4,687,777 ("the '777 patent"), claimed chemical compounds used to treat diabetes. These compounds were so closely related in structure to the closest prior art—a highly effective anti-diabetic compound repeatedly touted in the prior art—as to be presumed obvious under patent law. Petitioners demonstrated at trial that all of the compounds claimed in the '777 patent could have been made with routine modifications to that compound. But the Federal Circuit rejected an analysis based on the "objective reach of the claim" and instead required a showing that "***the prior***

art would have suggested making the specific molecular modifications" to achieve the claimed invention. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added). Does the standard that the Federal Circuit applied materially conflict with this Court's holding in *KSR*?

PARTIES TO THE PROCEEDING

This case arises from two separate challenges to the validity and enforceability of the '777 patent arising under the Hatch-Waxman Amendments to the Federal Food, Drug, & Cosmetic Act (collectively "the Hatch-Waxman Act"). *See* 21 U.S.C. § 355 et seq. The Hatch-Waxman Act allows generic pharmaceutical companies, such as Petitioners Alphapharm Pty., Ltd. and Genpharm Inc. (collectively "Alphapharm"), to certify their intent to seek marketing approval of a brand-name drug before patent expiry, so long as they certify that any patent listed by the brand-name pharmaceutical company as covering that drug, or a method of its use, is not infringed, invalid, or unenforceable. In return, the Hatch-Waxman Act allows the patent holder to file an infringement proceeding against the generic pharmaceutical company seeking such marketing approval.

Alphapharm certified that the compounds claimed in the '777 patent were obvious, and thus invalid, over the prior art. Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc. (collectively, "Mylan") also certified that the '777 patent was obvious. Respondents Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc. (collectively "Takeda") sued Alphapharm and Mylan in the Southern District of New York for infringement of the '777 patent. While the case was pending, Mylan also challenged the '777 patent as unenforceable as a result of Takeda's inequitable conduct before the Patent Office.

The case was tried in January 2006 before the bench. The district court ruled that the '777 patent was valid and enforceable. Alphapharm and Mylan appealed, and the Federal Circuit affirmed in separate decisions.

CORPORATE DISCLOSURE STATEMENT

The parent corporation and/or publicly held company that owns 10% or more of the stock of Petitioners Alphapharm Pty., Ltd. and Genpharm Inc. is Mylan, Inc. (Since the trial and appeal, Mylan Inc. acquired Alphapharm Pty., Ltd. and Genpharm Inc.)

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Alphapharm respectfully requests that this Court grant its petition for a writ of certiorari, reverse the judgment of the Federal Circuit, and enter judgment that claims 1, 2, and 5 of the '777 patent are obvious as a matter of law.

OPINIONS BELOW

The Federal Circuit's opinion is reported at *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), and is set forth in the appendix at A1-30. The opinion of the United States District Court for the Southern District of New York is reported at *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 417 F. Supp. 2d 341 (S.D.N.Y. 2006), and is set forth at A31-161.

JURISDICTION

The Federal Circuit entered judgment on June 28, 2007. (A168-69.) The Federal Circuit denied a combined petition for panel rehearing and rehearing en banc on September 27, 2007. (A170-71.) This Court has jurisdiction under 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS

This case relates to the obviousness statute set forth in 35 U.S.C. § 103(a):

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art

> are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

STATEMENT OF THE CASE

This petition raises a question of real legal significance: what is the proper standard to determine the structural obviousness of a chemical compound? The answer to this question affects every issued U.S. patent claiming chemical compounds, every pending application claiming chemical compounds, and every litigation where a claim reciting a chemical compound is at issue.

In April 2007, this Court rejected strict application of the Federal Circuit's TSM test because it was supported neither by the obviousness statute nor Supreme Court precedent. Section 103 requires that courts examine the differences between the subject matter sought to be patented and the prior art and make specific factual findings on the significance of these differences to the skilled artisan. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 15-17 (1966). If what is claimed is simply the product of routine innovation over the prior art, it is obvious under § 103. *KSR*, 127 S. Ct. at 1741. The closest prior art is naturally compared to the claimed invention, as the skilled artisan is presumed to know all of the pertinent prior art. *See, e.g., Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360-61 (Fed. Cir. 2007) (proceeding to find patent invalid as obvious from

the starting point of the closest prior art); *In re Huston*, 308 F.3d 1267, 1278 (Fed. Cir. 2002) (same). But here, the Federal Circuit reversed this analysis, and required that Alphapharm point to prior art that particularly motivated the skilled artisan to first select the closest prior-art compound, and then modify it in exactly the manner claimed. This was error and it provides ample basis for the Court to grant certiorari.

But the Court should grant certiorari for another reason. In applying the TSM test here, the Federal Circuit reasoned that some side effects from the closest prior-art compound would teach the skilled person away from making any modifications to it. But as Alphapharm demonstrated at trial—and as this Court recognized in *KSR*—this is precisely why the skilled artisan would make such changes. "[T]he claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement." *KSR*, 127 S. Ct. at 1740. Pharmaceuticals are expected to have effects in the body other than their indicated use. Reducing a side-effect profile is precisely the reason that skilled artisans make conservative substitutions in chemical compounds. (SA111.)

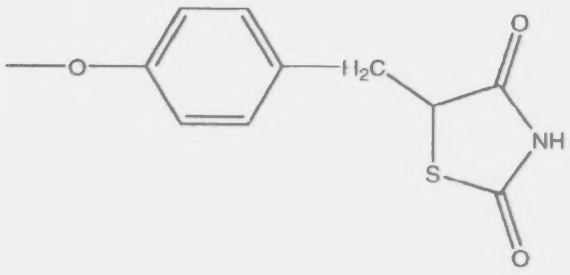
I. The Claimed Chemical Compounds and the Prior Art

This case concerns the chemical compound pioglitazone, which is used to treat Type 2 diabetes, and other related compounds claimed in the '777 patent. Type 2 diabetes is a condition where the body fails to utilize its insulin effectively, thereby resulting in unhealthy

blood sugar levels. In August 1987, the Patent Office issued the '777 patent. Takeda markets pioglitazone in the United States as the drug Actos®.

A. The Principal Antidiabetic Structure

The compounds claimed in the '777 patent are called thiazolidinediones ("TZDs"), which have been known for their antidiabetic properties since at least 1981 when Takeda's own U.S. Patent No. 4,287,200 ("the '200 patent") issued. The '200 patent disclosed a large number of TZD compounds, and touted their antidiabetic effects and "low toxicity" over the prior art. (SA28-37.) Shortly thereafter, Takeda disclosed that the antidiabetic properties of these compounds are related to the right-hand portion (or moiety) of the compound[1] as depicted below:



(SA54.) Takeda's work thereafter consisted of attaching various chemical structures to the left-hand side of the molecule to either minimize toxicity or optimize antidiabetic efficacy. (SA45-65.) Many of these structures are covered in the claims of the '200 patent.

---

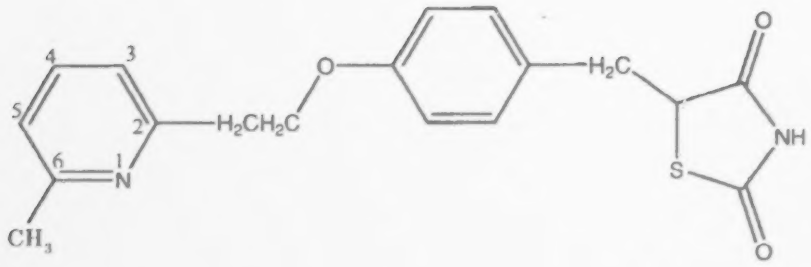
1. The pentagonal structure at the right of the figure depicted is known as a thiazolidinedione.

B. Compound b

In 1982, Takeda disclosed the efficacy results from its research into the structure-activity relationships on the left-hand side of TZDs in the prior-art reference, T. Sohda et al., "Studies in Antidiabetic Agents. II Synthesis of 5-4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4,dione (ADD-3878) and Its Derivatives." (hereinafter "Sohda II"). (SA45-65.) By the time the Sohda II reference was published, the most effective antidiabetic TZD compound in the prior art was set forth in Sohda II as compound 58 but labeled in this case as "compound b." (This compound was compared against pioglitazone and other compounds in a chart in the '777 patent, listing it as "compound b." The same name will apply here.) When prosecuting the '200 patent, for example, Takeda submitted an inventor declaration identifying the best nine compounds to overcome certain prior art cited by the examiner. (SA43.) Compound b's efficacy scores were higher than any other compound. (SA43.) No compound in Sohda II scored higher. (SA48-53.) Compound b is the closest prior-art compound to those claimed in the '777 patent. (A13.)

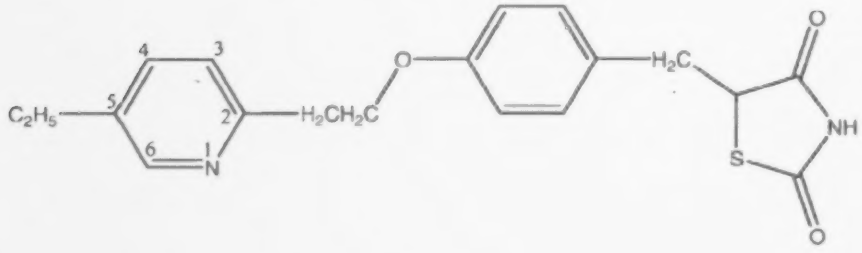
The left-hand side of compound b has a methyl (CH_3) group at what is called the "6 position" in organic chemistry parlance.

Compound b



The claimed compound, pioglitazone, is closely-related in structure to compound b:

Pioglitazone



Thus, compound b and pioglitazone differ only in the location and length of the group attached to the left-most ring known as a pyridyl. The structural similarity between compound b and the compounds claimed in the '777 patent could not be closer. The '777 patent includes claims drawn to an ethyl substituent at the 6-position—the same position as compound b. Extension by one carbon atom is the only difference between the claimed compounds and compound b. Pioglitazone is covered by claim 2 of the '777 patent, where the C_2H_5 group appears

at the 5 position. All of the compounds have the same antidiabetic properties, namely, lowering of serum glucose and triglycerides. Indeed, as noted by the Federal Circuit, the parties agreed that compound b was the closest prior art. (A13.)

C. Reason to Modify Compound b

The job of a medicinal chemist is to modify a given chemical compound to either improve its efficacy or decrease its toxicity. (SA111, ¶28.) Alphapharm presented evidence at trial demonstrating that compound b was an ideal candidate for routine tweaking based on Takeda's disclosures in the '200 patent (including its file history) and Sohda II. (SA111-13.) While compound b had the best efficacy of all the TZD compounds Takeda disclosed, it was not perfect. Sohda II remarked that the compound caused "considerable increases in body weight and brown fat weight." (SA54.) While brown fat weight was not a concern that affected human beings, body weight was. (SA84, pp. 910:17–911:9.) Alphapharm presented evidence at trial demonstrating that the medicinal chemist faced with a compound with superb efficacy but some side effects would make conservative changes to the compound, by substituting the 1-carbon methyl group with a 2-carbon ethyl group and moving that ethyl group to other potential places on the left-most ring of the compound. (SA111-12.) Adding a carbon atom to a group is called homologation. (SA111-12.) Moving a group around a ring is called ring-walking. (SA111-12.) Even Takeda's expert witnesses agreed that making such changes were well-known in medicinal chemistry at the time. (SA78-79;

SA88-89.) Indeed, Takeda taught the skilled artisan as much when it later sought patent protection for compound b, before the '777 patent was applied for. In that patent, U.S. Patent No. 4,444,779 ("the '779 patent"), Takeda disclosed that the constituent groups that the skilled artisan should use on available portions of the left-most pyridyl ring depicted above included "methyl, ***ethyl***, etc." (SA10, col. 2; ll. 43-45) (emphasis added.)

Takeda also admitted while prosecuting the '779 patent application that the earlier "problem" with compound b highlighted in Sohda II was no deterrent to patentability. Takeda argued to the examiner that compound b had become "especially" "important." (SA24.) Takeda also argued to the examiner that the class of substituted pyridyls was narrow, well-defined, and would have a predictable biological effect:

> the substituents in this case, ***actually cover a relatively narrow and well-defined group of constituents.*** Moreover, there should be no reason in the instant case for the Examiner to doubt that ***the claimed compounds having the specified substituent would function as a hypolipidemic and hypyglycemic (sic) agent as specified*** in the instant disclosure.

(SA26–27) (emphasis added.)

II. The District Court Decision

After a 13-day bench trial, the district court held the '777 patent valid. (A32-33.) But the district court's analysis was based on a flawed perception of the law of chemical obviousness:

> In the case of a chemical compound, a prima facie case of obviousness exists where there is a "structural similarity between claimed and prior art subject matter" ***and "the prior art gives reason or motivation to make the claimed compositions."*** *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000) (citation omitted).
>
> "[O]bviousness may render a claimed invention invalid where the ***record contains a suggestion or motivation to modify the prior art*** teaching to obtain the claimed invention." *Beckson*, 292 F.3d at 727. Thus, an invention is prima facie obvious where the prior art would imbue one of ordinary skill in the art with a "reasonable expectation of success" ***in achieving the goals that the inventor sought to accomplish*** by transforming a compound in the prior art into the structurally similar claimed invention. *Yamanouchi*, 231 F.3d at 1343 (citation omitted).
>
> * * *
>
> Where the creation of a chemical compound requires the chemist to pursue several steps in manipulating a compound revealed in the

> prior art, ***the patent challenger must show that one of ordinary skill in the art would have had sufficient motivation to take each of those steps.*** *Id.* at 1344-45.

(A93-94) (emphasis added.)

Based on its view of the law—more than one year before this Court's decision in *KSR*—the district court required Alphapharm to prove both a particular motivation to select the closest prior-art compound and a particular motivation to combine the prior art to obtain the claimed pioglitazone—or one of the ethyl-substituted TZDs. (A96.) Nothing in § 103 or this Court's precedents requires proof of either.

The district court further held that "the prior art did not disclose or suggest either the pioglitazone molecule itself or how to make it." (A96.) And the district court held that one skilled in the art would not have "chosen compound b as a lead compound," finding that Alphapharm failed to prove that a skilled artisan would "have had sufficient motivation" to make the simple substitutions Takeda itself taught in the '779 prior-art patent. (A96.)

In analyzing the prior art, the district court determined that one of skill in the art would not have been motivated to select compound b as a lead compound—the undisputed closest prior art—because Sohda II "taught away" from compound b owing to the side effects of brown fat and weight gain. (A104-08.)

Alphapharm appealed the district court's validity ruling to the Federal Circuit.

III. The Federal Circuit's Affirmance

The Federal Circuit affirmed. Although it recognized that *KSR* clarified the law of obviousness, the Federal Circuit required: (1) proof that the skilled person would have found the specific reason in the prior art for selecting the closest prior art as a lead compound; and (2) proof that the ***"prior art would have suggested making the specific molecular modifications"*** to achieve the claimed compound in exactly the manner claimed. (A11) (emphasis added.) In applying this test here, the Federal Circuit held that "the closest prior art compound (compound b, the six-methyl) exhibited negative properties that would have directed one of ordinary skill away from that compound." (A18.)

Alphapharm moved for a petition for rehearing and rehearing en banc but the Federal Circuit denied those petitions. (A170-71.)

REASONS FOR GRANTING THE PETITION

I. The Federal Circuit's Affirmance Conflicts with *KSR*'s Flexible Approach Because it Rigidly Applied the "Teaching, Suggestion, or Motivation" Test

The law presumes that structurally similar compounds —especially when used for the same purpose in the prior art—are prima facie obvious. This presumption arises because the law recognizes that structurally similar compounds are presumed to have similar properties. *In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985) ("when chemical compounds have 'very close' structural similarities and similar utilities, ***without more*** a *prima facie* case may be made.") (bold emphasis added). This comports with this Court's "common sense" approach stated in *KSR*. *KSR*, 127 S. Ct. at 1742.

"[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness." *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc); *see also In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995). The prior art repeatedly taught that substituted TZDs had antidiabetic properties and low toxicity. But the Federal Circuit additionally required particular explicit motivation in the prior art to both select the closest prior art and to modify it in specific ways. Such a test is inconsistent with *KSR*, as it would impose a particular TSM requirement in every chemical obviousness case. This rigid application is just the type of analysis the Supreme Court rejected in *KSR*.

A. This Rigid Chemical Obviousness Test Requires a New and Onerous Requirement for Obviousness—Motivation to Find the Closest Prior Art

In *KSR*, this Court ruled that the TSM test while capturing a "helpful insight," may at times be inconsistent with the obviousness inquiry. *KSR*, 127 S. Ct. at 1741. Section 103 of Title 35 does not focus on how the prior art would motivate the skilled artisan to reach the invention. *Id.* Rather, for obviousness,

> [w]hat matters is the ***objective reach of the claim***. If the claim extends to what is obvious, it is invalid under § 103. One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

Id. at 1742 (emphasis added).

The obviousness analysis starts—not with the prior art and what motivated the skilled person—but with the claims. Courts must examine what is claimed and then determine whether the person of ordinary skill in the art could attain the invention using ***any*** predictable means from the closest prior art. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986) (noting that the skilled artisan is presumed to be aware of ***all*** prior art.) For example, in *KSR*, the patent at issue [Engelgau] covered adjustable automobile pedals with an electronic sensor to detect the position of the pedal and transmit that position to a computer-controlled throttle. *KSR*, 127 S. Ct. at 1736-37. The Asano patent was the closest prior art, and

covered each element of the Engelgau claims but not the use of a sensor. *Id.* at 1738. This Court did not analyze why the skilled person would select Asano from the prior art. Instead, the analysis focused on whether the Asano design "provided an obvious example of an adjustable pedal with a fixed pivot point." *Id.* at 1742. It was of no importance that Asano was designed to solve another problem that might deter the skilled person. As this Court acknowledged, "a person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id.*

Here, the Federal Circuit failed to perform an analysis based on the objective reach of the claim. Rather, Alphapharm was required to prove in the first instance why a person of skill would select compound b as the best compound from the prior-art compounds available. (A13-14.) This departure from *KSR*'s holding is evident throughout the district court's opinion (adding bold italics):

> The prior art did not ***disclose*** or suggest either the pioglitazone molecule itself or how to make it. (A96);
>
> To begin with, the evidence is overwhelming that one skilled in the art would not have, based on the prior art, chosen compound (b) as ***a lead compound***. (A96);
>
> The discussion that follows examines each of the Graham factors, ***paying particular attention to the identification of a lead compound***, the motivation to alter that compound, and unexpected results. (A97);

and the Federal Circuit's opinion (adding bold italics):

> By "lead compound," we understand Alphapharm to refer to a compound in the prior art that would be ***most promising to modify***. . . . (A13);
>
> The court, however, found nothing in the '200 patent, . . . to suggest to one of ordinary skill in the art that those nine compounds . . . were the ***best performing compounds*** as antidiabetics. . . . (A14.)

Curiously, the Federal Circuit's decision to require specific proof that the skilled person would select compound b as the best compound in the prior art was contrary to that court's own precedent. For example, in *In re Fulton*, the court held that the prior art need not teach that a particular combination is "preferred" or "optimal" to be obvious. 391 F.3d 1195, 1201-02 (Fed. Cir. 2004). Alphapharm never had to prove that compound b was the best compound or that no other routes were available. *Id.* at 1202. Rather, "'the question is whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination.'" *In re Beattie*, 974 F.2d 1309, 1311 (Fed. Cir. 1992) (emphasis in original). The prior art here both showed methyl and ethyl substituted-TZDs were promising. The '779 patent focused specifically on methyl ***and ethyl*** substitutions on the left-hand pyridyl ring of TZD compounds. (SA10 at col. 2, ll. 40-45.) Indeed, Takeda represented to the Patent Office that one such example, compound b, had become "especially" "important." (SA24.)

Nothing in the science of medicinal chemistry or any of the chemical arts supported the Federal Circuit's requirement that a lead compound be the "most promising to modify." (A13.) A lead compound need not be the "leading" or the best. Rather, a lead compound is one that has desired activity but some deficits. (SA111.)

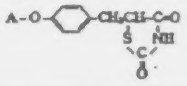
There can be no question of harm here. Given the departure from the *KSR* analysis, the Federal Circuit (and the district court) could never reach the threshold inquiry required. "A court must ask whether the improvement [over the closest prior art] is more than the predictable use of prior art elements according to their established functions." *KSR*, 127 S. Ct. at 1740. Under that standard, the compounds claimed in the '777 patent are clearly obvious.

1. The Proper Analysis Under *KSR* Demonstrates that the Claims of the '777 Patent Would Have Been Obvious

A compound is obvious where "the claimed subject matter [involves] the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement." *KSR*, 127 S. Ct. at 1740. A patent challenger need only point to the availability of a compound in the prior art that gave the skilled artisan "an apparent reason to combine the known elements in the fashion claimed." *Id.* at 1741. Here, the prior art repeatedly promoted substituted TZDs, including methyl and ethyl substitutions, and thus provided a reason to modify compound b with homologation and ring-walking to arrive at the claimed pioglitazone.

Alphapharm demonstrated the reason to modify at trial. One structural difference separates the ethyl genus claimed in the '777 patent and compound b—a C_2H_5 rather than a CH_3 at the 6-position on the ring. Two structural differences separate pioglitazone and compound b. Takeda added a CH_2 group to the methyl (CH_3) on the pyridyl ring of compound b and moved the resulting ethyl one position over on the ring—from the 6 position to the 5 position. Because compound b was already known as the most efficacious antidiabetic compound in the prior art—but with some side effects—the skilled person had a reason to make these minor changes. (SA43.) In the following table excerpt, compound b is referred to as compound 58. The data in Takeda's own Sohda II reference demonstrated that the triglyceride-lowering potency doubled when a methyl substituent was added to the unsubstituted pyridyl ring (shown as compound 57) to obtain compound 58. In the table, the higher the score, the greater the potency (A48-49):

TABLE IV. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	A	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Hypoglycemic activity[e]	Plasma triglyceride-lowering activity[f]
56		B	55.6	183–184	C–M	$C_{16}H_{16}N_2O_3S$	3	3
57		B	55.4	209–210	DMF–W	$C_{17}H_{16}N_2O_3S$	3	2
58		B	42.7	103–104	EA–H	$C_{18}H_{18}N_2O_3S \cdot 1/2H_2O$	3	4
59		B	51.6	175–176	C–M	$C_{17}H_{16}N_2O_3S$	[illegible]	[illegible]
60		B	77.6	176–177	C–M	[illegible]	3	2

Addition of a single CH_3 group doubled lipid-lowering activity from 2 to 4.

(SA51.) The skilled artisan would have understood that any attempt to maintain the activity of compound 58 (i.e., compound b) would require ameliorating the compound's side effects by making conservative changes to the pyridyl ring, substituting with methyls and ethyls at the four available places on the ring (i.e., the 3, 4, 5, and 6 positions). (SA112.)

Moreover, Takeda had provided in the prior art the very instruction for making these changes. Takeda had sought coverage of substituted pyridyls (including pioglitazone) in its prior-art '779 patent. There, Takeda taught the skilled artisan homologation and ring-walking on the pyridyl ring with ethyl substituents: "***As examples of such substituents may be mentioned lower alkyls (e.g. methyl, ethyl, etc.)***. . . ." (SA10 at col. 2, ll. 44-45) (emphasis added.)

All of the compounds could have been achieved by applying conventional techniques in medicinal chemistry to improve the profile of known chemical compounds, including homologation and ring-walking. Applying homologation to improve the profile of the prior-art compound b would have invalidated claims 1 and 5 of the '777 patent. Applying the well-known technique of ring-walking would have invalidated claim 2, the claim drawn to pioglitazone. (SA113.) As this Court observed in *KSR*, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 127 S. Ct. at 1740. There can be no argument that homologation and ring-walking were beyond the purview of the skilled artisan.

Takeda's reasoning in the '779 patent—that substituted TZDs including methyl and ethyl substitutions are promising antidiabetic compounds, and that compound b is especially so—gives the skilled artisan the reason to synthesize and test the compounds claimed in the '777 patent, just as *KSR* urges.

2. Takeda Admitted that Adding Substituents to the Pyridyl Ring Would Have Resulted in Compounds with the Same Antidiabetic Effect

A design need existed to solve a problem—minor side effects associated with compound b. The number of possible solutions, based on Takeda's admissions, was quite small. The district court found, and the Federal Circuit affirmed, that "thousands" of possibilities existed. (A107; A19-20.) But methyl and ethyl substituents can exist at only four locations on the pyridyl ring in question resulting in seven variants (excluding compound b because it is prior art). (SA114.) Under *KSR*, the only remaining inquiry is whether the solutions are predictable. Here, Takeda itself admitted that predictability in the '779 patent prosecution history: "the substituents in this case, actually cover a relatively narrow and well-defined group of constituents . . . [that] would function as a hypolipidemic and hypyglycemic (sic) agent as specified in the instant disclosure." (SA26-27.) The skilled person was thus taught that making such conservative changes would not affect the compound's antidiabetic use. *See also McNeil-PPC, Inc. v. Perrigo Co.*, — F. Supp. 2d —, No. 05-1321, 2007 WL 1933931, at *8 (S.D.N.Y. July 7, 2007) (finding drug patent obvious in light of, among other things, the inventor's admissions).

The Federal Circuit also affirmed the nonobviousness of the other claims in the '777 patent reciting ethyl-substituted pyridines in positions 3, 4, and 6. (A28.) But Judge Dyk, in his concurrence, found that claims 1 and 5, which also covered pioglitazone, were so broad as to be "likely invalid." (A28.) Nowhere in the '777 patent is there any evidence that these other ethyl-substituted compounds would even be active. The table evidencing activity for these compounds is based entirely on activity in pioglitazone. (SA5.) Takeda clearly relied on the common sense of the skilled artisan, who was expected to understand that these other ethylated compounds had predictable activity, i.e., a "broad safety margin" similar to pioglitazone's. (SA3, col. 1, l. 37.)

Under *KSR*, no compound can receive patent protection where it represents nothing more than "the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement." *KSR*, 127 S. Ct. at 1740. Alphapharm amply demonstrated the obviousness of the claimed compounds under *KSR*. Only by ignoring the proper inquiry—and requiring as an additional prerequisite the specific motivation for the skilled person to select the closest prior art and receive particular instructions on modification—was the panel able to affirm nonobviousness.

B. The Prior Art Did Not Teach Away from the Claimed Invention

In affirming the district court, the Federal Circuit agreed that Sohda II's statements about compound b's brown-fat and weight-gain effects "taught away" from compound b. (A17.) But where the claimed invention does not exhibit "markedly superior" properties over the prior art, the claim is obvious. *In re Coes*, 173 F.2d 1012, 1014 (C.C.P.A. 1949) (invalidating claims to adjacent homologues in the prior art).

Here, by overemphasizing the side effects of compound b noted in Sohda II, the district court turned a deaf ear both to Takeda's later representations in the '779 patent to use methyl and ethyl groups on the left-most pyridyl ring, and the overwhelming similarities in both structure and properties between compound b and pioglitazone. (A106-07.) For instance, Takeda obtained the '779 patent covering substituted pyridyls—and compound b in particular—based on the assertion that compound b had become "especially" "important." (SA24.) Takeda vitiated any argument that compound b was "unlikely to be productive of the result sought"—the test for teaching away—when Takeda obtained the '779 patent and drew a specific claim to that compound and other lower-alkyl substituted TZDs. (SA19.) *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

In any event, Takeda's expert witness and fact witnesses from its development partner, Upjohn, admitted that any concerns about brown fat in Sohda II were speculative when it comes to human beings, and

weight gain was a sign that the compound was working. (SA71; SA129; SA84.) These admissions demonstrate that the comments in Sohda II on compound b's side-effect profile would not have precluded the skilled artisan from selecting that compound—even if Takeda had chosen not to patent this "especially" "important" compound. (SA24.)

In *KSR*, the Supreme Court cautioned lower courts against making such errors. 127 S. Ct. at 1740. "Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it." *Id.* at 1742-43. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* at 1742. The skilled artisan piecing together Takeda's later representations would, at the very least, have reason to create the lower-alkyl (e.g., methyl and ethyl) substituted TZDs Takeda expressly taught in the '779 patent. And the '779 patent demonstrated that Takeda had singled out compound b as an especially important compound. Indeed, compound b was a lead compound for Takeda during this time frame. (SA91) (noting that pioglitazone, labeled ADD-4833, was a peripheral compound of compound b, labeled ADD-3959.)

Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc., 471 F.3d 1369, 1378 (Fed. Cir. 2006), *cert. denied*, 128 S. Ct. 146 (2007), relied upon below by Takeda, is not on point. *Eli Lilly* concerned the validity of Eli Lilly's patent directed to olanzapine—a compound used to treat schizophrenia. *Id.* at 1373. The challenger alleged that olanzapine was obvious over its closest structural

relative, ethyl-olanzapine. *Id.* at 1377-78. Ethyl-olanzapine and olanzapine are homologs of each other, as here. *Id.* at 1379.

But the similarity between *Eli Lilly* and this case stops at structure. The closest prior art in *Eli Lilly* was "less active" as an antipsychotic drug than olanzapine. *Id.* at 1379. In *Eli Lilly*, ***all*** of the prior art taught away from selecting an adjacent homolog as a lead compound. *Id.* at 1377-78. All of the references taught that an electron-withdrawing element was necessary, i.e., halogens such as fluorine, not ethyls. *Id.* at 1378. This Court's denial of the petition in *Eli Lilly* is certainly understandable. The closest prior art was well-outside the "objective reach of the claim" to olanzapine, and therefore nonobvious. *KSR*, 127 S. Ct. at 1742.

The contrast to this case could not be more stark. The closest prior art to pioglitazone was compound b, a compound that the prior art repeatedly quantified as the most potent antidiabetic. Not once, but at least four times in the prior-art period Takeda expressly promoted the potent antidiabetic activity of compound b: (1) in the '200 patent (SA30, col. 1, ll.4-6); (2) in an inventor declaration submitted as part of the '200 patent's prosecution history (SA43); (3) in Sohda II where compound b was shown to have double the potency than an unsubstituted pyridyl ring (SA48-53); and (4) when Takeda claimed compound b in the '779 patent as a pharmaceutical composition used to treat diabetes (SA19, claims 4, 6). A skilled artisan would not have missed these pronouncements in her review of the prior art.

II. Allowing the Federal Circuit's Application of the "Teaching, Suggestion, or Motivation" Test to Stand May Affect Thousands of Other Similarly Situated Cases

The TSM test as applied here forces a challenger to prove particular motivation in the prior art to select and modify the lead compound, which as asserted above, applies a rigid approach to structural obviousness and adds an onerous new motivation requirement for any challenger. Here, the Federal Circuit claimed that its requirement that Alphapharm show a motivation to select and modify a lead compound was "deciding the appeal as it has been argued." (A13.) But it is the province of the Federal Circuit to decide the case as the law requires. Here, the law required the Federal Circuit to decide the obviousness inquiry while following the strictures outlined in *KSR*. That is all the more important when the Federal Circuit's own law had been inconsistent with Supreme Court precedent and § 103 for many years, including those years this case was litigated and tried.

The Federal Circuit also created a dangerous precedent for all chemical obviousness cases concerning pharmaceuticals. Before this case, the standard for "teaching away" was strict. The prior art taken as a whole only taught away when the route to the invention was "unlikely to be productive of the result sought." *Medichem*, 437 F.3d at 1165. But the Federal Circuit appears to have abandoned that precedent, in at least chemical-compound cases, allowing teaching away even when the pioneer company obtains a patent on a compound using the route most promising—but not without side effects—from the prior art.

Pharmaceuticals are expected to have effects in the body other than their indicated use. It is the role of the medicinal chemist to reduce those effects to acceptable levels while maximizing efficacy. Now, under the evidently relaxed Federal Circuit patentability standard in this case, even the most minor side effect reported in the literature will be touted by a patentee as teaching the skilled person away from the invention. The result will be routine innovation in pharmaceuticals covered by patent monopolies at the expense of the public.

By addressing these missteps now, the Court will clarify and advance the progress of every issued U.S. patent claiming chemical compounds, every pending application claiming chemical compounds, and every litigation where a claim reciting a chemical compound is at issue. It is for these reasons that the Court should grant Alphapharm's petition.

CONCLUSION

Alphapharm respectfully requests that this Court grant the petition for a writ of certiorari, reverse the judgment of the Federal Circuit, and enter judgment that claims 1, 2, and 5 of the '777 patent are obvious as a matter of law.

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Respectfully submitted,

EDGAR H. HAUG
Counsel of Record
KEVIN MURPHY
JEFFREY A. HOVDEN
DAVID A. ZWALLY
FROMMER LAWRENCE & HAUG LLP
745 Fifth Avenue
New York, New York 10151
(212) 588-0800

Attorneys for Petitioners